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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,357	04/15/2004	Najib Babul	2039.0010001	6312
23280 7590 11/15/2007 DAVIDSON, DAVIDSON & KAPPEL, LLC 485 SEVENTH AVENUE, 14TH FLOOR NEW YORK, NY 10018			EXAMINER KIM, JENNIFER M	
			ART UNIT 1617	PAPER NUMBER
			MAIL DATE 11/15/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/824,357	BABUL, NAJIB	
	<b>Examiner</b>	<b>Art Unit</b>	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on September 13, 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) 15,16,18,19 and 32-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14, 17, 20-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All   b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/15/06;7/28/04</u>   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

Applicant's election without traverse of claims drawn a method of treating or preventing pain comprising administering to a subject in need of pain treatment or pain prevention (a) one or more analgesics and (b) one or more beta adrenergic agonist, classified in class 514, subclasses 165, 282, 406, 471, 569 and 570 with species of opioids as an analgesic is acknowledged. Accordingly, claims 1-14, 17, 20-31 have been examined only to the extent of Applicants' elected species. Claims 15, 16, 18, 19 and 32-40 have been withdrawn from consideration since they are non-elected invention.

### ***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-14, 17 and 20-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treating pain", does not reasonably provide enablement for the "preventing pain". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

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3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

**Nature of the Invention:** All of the rejected claims are drawn to a method of treating or preventing pain comprising administering to a subject in need of pain treatment or pain prevention (a) opioids and (b) beta adrenergic agonist. The nature of the invention is complex in that it encompasses the actual prevention of pain (e.g. cancer pain) such that the subject treated with above compounds does not contract pain.

**Breadth of the Claims:** The complex of nature of the claims greatly exacerbated by breadth of the claims. The claims encompass preventing pain in humans which has potentially many different causes (i.e. many different medical disorders, drug side-effects (chemotherapeutic agents, radiation or surgery, etc..). Each of which may or may not be addressed by the administration of the claimed compounds.

**Guidance of the Specification:** The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually prevent pain is minimal. All of the guidance provided by the specification is directed towards treatment rather than prevention of pain.

**Working Examples:** All of the working examples provided by the specification are directed toward the treatment rather than prevention of pain.

**State of the Art:** While the state of the art is relatively high with regard to treatment of painful disorder (i.e. cancer pain), the state of the art with regard to prevention of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to prevent development of pain. State of the Art, Shantha (U.S. Patent No. 5,735,817) teaches that painful conditions, which affect our body, are **difficult to treat**, and it is especially true of most cancer pain. In some types of advanced cancers, the pain **cannot be alleviated** by any known method. Shantha also teaches that even with **hundreds of milligrams of morphine** administration, the **pain could not be relieved**. (column 1, lines 1-30). State of the Art, Davar (U.S. Patent No. 6,667,832 B1) also teaches that the **cancer pain is often debilitating and difficult to treat**, especially in patients with advanced disease and the pain treatment often requires very large doses of either systemic or intraspinal opioids, often an insufficient pain treatment that produced undesirable side-effect. (column 1, line 62- column 2, line 10). Therefore, it is highly speculative that the active compounds would actually "prevent" the pain condition that is considered to be difficult in the treatment process.

**Predictability of the Art:** The lack of significant guidance from the specification or prior art with regard to the actual prevention of pain in a human subject with

the claimed compounds makes practicing the claimed invention unpredictable in terms of prevention of pain.

**The amount of Experimentation Necessary:** In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for prevention of pain. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard prevention of pain with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding prevention of pain with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of pain in a subject by administration of one of the claimed compounds.

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Therefore, a method of treating or **preventing** pain comprising administering to a subject in need of pain treatment or pain **prevention** (a) opioids and (b) beta adrenergic agonist is not considered to be enabled by the instant specification.

4. Claims 1-14, 17 and 20-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treating pain comprising administering the specific opioid (i.e. morphine) and the specific beta adrenergic agonist (i.e. albuterol) ", does not reasonably provide enablement for the "treating pain administering opioids and beta adrenergic agonists". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. All of the rejected claims are drawn to a method of treating or preventing pain comprising administering to a subject in need of pain treatment or pain prevention **(a) opioids and (b) beta adrenergic agonists providing enhanced effect**. The nature of the invention is complex in that it encompasses the various opioids and beta adrenergic agonists that are structurally different such that the subject treated with above compounds enhancing analgesic effect in pain treatment.

The guidance given by the specification as to how one would actually practice the invention of preventing pain with **any opioid and any beta-adrenergic agonist** is minimal. All of the guidance of the working examples are directed to the employment of specific opioid (morphine) and the specific beta-adrenergic agonist (albuterol). The

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specification teaches how to treat pain with the specific combination of the active agents (albuterol and morphine) in a subject however, there are no working examples, prophetic or otherwise in the specification how to actually treat pain with the enhanced effect with all of the claimed opioids and beta-adrenergic agonists. The state of the art with regard to determining the enhanced analgesic effect of the combination of any opioids and any beta-adrenergic agonists in a subject is not predictable. Given the complex nature of the invention, which involves enhanced analgesic effect with any opioids and any beta-adrenergic agonists in the breadth of the claim, the complete lack of guidance from the specification regarding how to interpret the data generated a single combination, minimal of working example as such, the uncertainty of whether the current state of the art regarding the use of such formulations would actually result in enhanced analgesic effect with any combination of opioids and beta-adrenergic agonists. It would take undue, unpredictable experimentation to practice applicant's invention to treat pain with combination of opioids and beta-adrenergic agonist produces enhanced analgesic effect. Therefore, a method of treating or preventing pain comprising administering to a subject in need of pain treatment or pain prevention **(a) opioids and (b) beta adrenergic agonists providing enhanced effect** is not considered to be enabled by the instant specification.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:



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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-14, 17, 20-24 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Breton et al. (U.S. Patent No. 5,958,432) and Naftchi et al. (1981).

Breton et al. teach that beta-adrenergic agonist including salbutamol, isoproterenol, CGP1217, nylidrin, salmeterol, fenoterol, terbutaline or pirbuterol are substance P antagonists, which are involved in the transmission of pain. (column 2, lines 28-31, and column 1, lines 45-50, column 3, lines 9-15).

Naftchi et al. suggest that morphine analgesic is due to inhibition of intraneuronal substance P release in regions. (abstract).

The claims differ from the cited references in claiming combination of opioids, and beta-adrenergic agonist, to treat pain. To employ combinations of opioids and beta adrenergic agonist to treat pain would have been obvious because all the components are well known individually for treating pain. It would be expected that the combination of components would treat painful conditions as well. The motivation for combining the components flows from their individually known common utility.

As stated in In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

Therefore, it would have been prima facie obvious to combine opioid and beta-adrenergic agonist conjointly in a formulation to treat pain. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Claims 25, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Breton et al. (U.S. Patent No. 5,958,432) and Naftchi et al. (1981) as applied to claims 1-14, 17, 20-25 and 28-31 above, and further in view of Malmqvist-Granlund et al. (U.S. Patent No. 5,178,868).

The teachings of Breton et al. and Naftchi et al. as applied as before.

Breton et al. and Naftchi et al. do not teach the oral administration.

Malmqvist-Granlund et al. teach that morphine and salbutamol (also known as albuterol) can be formulated as an oral formulation.

It would have been obvious to one of ordinary skill in the art to modify the obvious combination of opioid (morphine) and salbutamol as modified by Breton and Naftchi et al. in a single oral formulation because each of the active agents are suitable for the oral administration as taught by Malmqvist-Granlund et al. One would have been motivated to make such a modification in order to provide most convenient analgesic therapy by oral administration. There is a reasonable expectation of orally administering the obvious combination modified by Breton and Naftchi et al. because each of the active agents are suitable in oral dosage form as taught by Malmqvist-Granlund et al.

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Claims 1-14, 17 and 20-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brochet et al. (1986).

Brochet et al. teach antinociceptive activity of beta-adrenoreceptor agonists including isoproterenol, clenbuterol and salbutamol (also known as albuterol). (title, abstract, under discussion. Brochet et al. teach that these agents exerted an antinociceptive activity on the hot plate test in mice.

Brochet et al. lack opioids, amounts of salbutamol, the oral administration and mechanisms of action set forth in claims 5-8 and 11-13.

It would have been obvious to one of ordinary skill in the art to modify the teaching of Brochet et al. and incorporate opioids for the treatment of pain because beta-adrenoreceptors such as albuterol is well known by Brochet et al. for having antinociceptive effect and because it is well within the knowledge of one of ordinary skill in the art to combine another analgesic compound such as opioids to achieve at least an additive effect.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in *Crockett*, the idea of combining them flows logically from their having been individually taught in the prior art.

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Therefore, it would have been prima facie obvious to combine opioid and beta-adrenergic agonist conjointly in a formulation to treat pain. Further, no unobviousness is seen in the effective amounts and dosage formulation claimed because once the usefulness of a compound is known to treat a condition, it is within the skill of the artisan to determine the optimum ratio and suitable dosage forms for an individual patient being treated. Further, the mechanism by which the active ingredient gives the pharmacological effect does not alter the fact that the obvious method of Brochet et al. to obtain the same pharmacological effects which would result from the claimed method. The patient, condition to be treated and the effect are the same. An explanation of why that effect occurs does not make unobvious the treatment of the conditions encompassed by the claims.

It is suggested that Applicant submit a declaration to clearly establish a surprising and unexpected result using Applicant's teaching.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

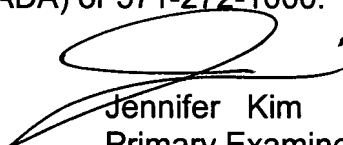
None of the claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Jennifer Kim  
Primary Examiner  
Art Unit 1617

Jmk  
October 30, 2007